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CHEMICAL TRANSGLYCOSYLATION OF OCTOSYL ACID

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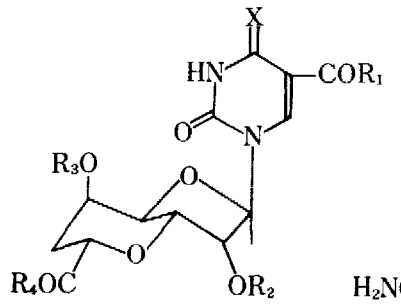
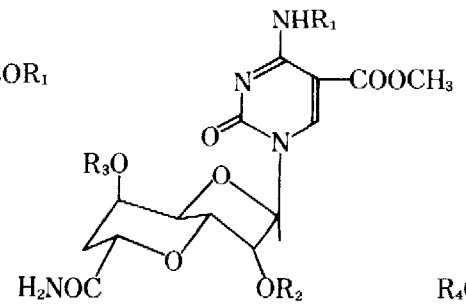
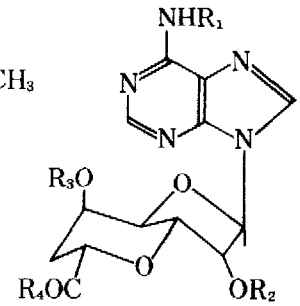
In a previous communication,[1] we have reported the isolation and the structure of anhydrooctose uronic acid nucleosides, octosyl acids, which are metabolites of *Streptomyces cacaoi* var *asoensis* Since these nucleosides were regarded as carboanalogs of 3',5'-cyclic nucleotides, it was especially interesting to convert the 5-substituted uracil base of octosyl acids into adenine to prepare an analog of biologically important cyclic AMP. Transglycosylation of pyrimidine nucleosides to purine nucleosides was described before by Miyaki *et al* [2] However, since their procedure was not mild enough to apply to the labile sugar skeleton of octosyl acids,[1] we studied a more efficient method, utilizing N^6-benzoyl,9-bis(trimethylsilyl)adenine and trimethylsilyl perchlorate as a catalyst in







1 $R_1=R_4=OH$, $R_2=R_3=H$, X=O

2 $R_1=R_4=OMe$, $R_2=R_3=Ac$, X=O

3 $R_1=R_4=OMe$, $R_2=R_3=Ac$, X=S

4 $R_1=R_2=R_3=H$

5 $R_1=R_2=R_3=Ac$

6 $R_1=Bz$, $R_2=R_3=Ac$, $R_4=NH_2$

7 $R_1=R_2=R_3=H$, $R_4=OH$

dichloroethane—acetonitrile. This modification is based on a recent report by Vorbruggen and Krolikiewicz[3] concerning new catalysts for nucleoside synthesis.

Octosyl acid A (1) was esterified followed by acetylation to give the dimethylester diacetate (2), mp 229-231°. Thiation of 2 with phosphorous pentasulfide in dioxane[4] afforded the 4-thiouracil derivative (3), mp 206-208°, which on treatment with 20% ammoniacal methanol at 100° yielded a cytosine derivative (4), mp 290-293°(dec), $C_{14}H_{18}N_4O_8 \cdot H_2O$[5] in good yield. Acetylation of 4 yielded triacetyluronamide (5), mp 164-171°. Mass spectrum (70 eV, LKB 9000S instrument): M, *m/e* 496 (0.5% relative intensity); sugar, 286 (32); base + CH_2O,[6,7] 240 (14); base + 2H, 212 (94), sugar - HOAc - Ac, 183 (59); base + 2H - CH_2CO, 170 (100), sugar - 2HOAc, 166 (94).

Transglycosylation to form an adenine nucleoside was performed as follows. To an acetonitrile solution (10 ml) of 5 (1.0 mmole) was added a solution of N^6-benzoyl,9-bis(trimethylsilyl)adenine[8] (2.0 mmoles) in 4.5 ml of dichloroethane, followed by addition of 1.2 mmoles of trimethylsilyl perchlorate[9] in 2 ml of dichloroethane. The solution was refluxed for 20 hr After work-up of the reaction mixture with a cold dichloroethane—aqueous sodium bicarbonate, followed by silica gel chromatography in the solvent, chloroform—methanol (50 1), an adenine derivative, 9-β-(3,7-anhydro-6-deoxy-2,5-*O*-diacetyl-D-*glycero*-D-*allo*-octofuranosyluronic acid)-N^6-benzoyladenine (6) was obtained in 60% yield as a crystalline powder Uv max (EtOH): 231, 279 nm (ε 13,400, 19,200), $[\alpha]_D^{20}$ = + 10.0° (*c* 1 24, $CHCl_3$) Mass spectrum (70 eV) M, *m/e* 524 (2 7% relative intensity), M - H - CO, 495 (16); sugar, 286 (18); base + CH_2O, 268 (9); base + 2H, 240 (45), 210 (28); sugar - HOAc - Ac, 183 (6.2), sugar - 2HOAc, 166 (32); C_6H_5CO, *m/e* 105 (100). Pmr ($CDCl_3$) δ 1 86 (m, 1, H-6'a), 2.56 (m, 1, H-6'e), 1.99, 2.21 (s, 3H each, CH_3COO), 4 01 (q, 1, H-4'), 4.53 (q, 1, H-7'), 4.97 (q, 1, H-3'), 5 68 (broad, 1, H-5'), 5 71 (d, 1, H-2'), 6.03 (s, 1, H-1'), 6.12, 6 43 (broad, 1H each, $CONH_2$), 7.4—7 7, 7 9—8.1 (m, 5, benzoyl H), 8.07, 8.78 (s, 1H each, H-2 and H-8), 9 31 (broad s, 1, 6-N*H*Bz); $J_{1',2'}$ = 0, $J_{2',3'}$ = 6.0, $J_{3',4'}$ = 10.0, $J_{4',5'}$ = 3 0, $J_{5',6'e}$ = $J_{5',6'a}$ = ∿3, $J_{6'a,7'}$ = 12.5, $J_{6'e,7'}$ = ∿3 Hz.

Treatment of 6 with 0 2 *N* sodium methoxide in methanol, followed by 0 5 *N* sodium hydroxide afforded a crystalline free nucleoside 7 in 80% yield; mp >280°, $C_{13}H_{15}N_5O_5 \cdot H_2O$.[5] Uv max: H_2O, 260 nm (ε 12,700); 0.05 *N* HCl, 257 (12,500); 0.05 *N* NaOH, 260 (13,000) $[\alpha]_D^{20}$ = - 35 0° (*c* 0.3, *N* NH_4OH). CD min (H_2O): $[\theta]_{260}$ = - 8830. Pmr (1% ND_4OD) · 6.30 (s, 1, H-1'), 8.36, 8.42 (s, 1H each, H-2 and H-8).

The mass spectrum of the final product 7 after trimethylsilylation[10] is shown in Figure 1. Assignments of the principal peaks follow those for silylated nucleosides[11] and confirm the presence of adenine and octosyl acid sugar moieties M (tetrasilyl derivative), *m/e* 625, M - CH_3, 610, sugar - H, 418; sugar - CO, 390; 418 - TMSOH, 328, base + C_2H_3OTMS, 322; 390 - TMSOH, 300;

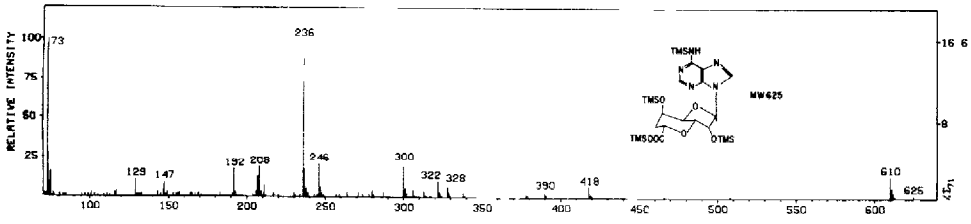


Figure 1 Mass spectrum of the trimethylsilyl derivative of 7

$C_4H_4O_3(TMS)_2$, 246, base + CH_2O, 236, base + 2H, 208; base + H - CH_3, 192; $SiMe_3$, 73.

A sharp singlet of anomeric protons in pmr of 6 and 7 proves the intact 3,7-anhydrooctofuranose uronic acid skeleton[1] as well as β-orientation of the nucleoside bond.[1,2] No appreciable amount of α-anomer was observed. The negative Cotton effect observed in 7 indicates the *anti* conformation

This improved transglycosylation reaction may prove to be a versatile method for the interconversion of purine, pyrimidine, and analogous *N*-nucleosides. This line of study is currently in progress in this laboratory. Biological activity of 7 is also under investigation.

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